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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	21

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/559,013	Ono et al	
Examiner	Art Unit	
CANELLA	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☑ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims 64, 66, 68, 69, 71, 72, 75, 76, 79, 86, 90, 97, 101, 105, 108, 113, 119, 122-137

4) ☐ Claim(s) 1, 2, 6, 15, 19, 36, 38, 41, 47, 53, 54, 56, 60, 62 is/are pending in the application.

4a) Of the above, claim(s) 1, 2, 6, 36, 38, 47, 53, 68, 69, 71, 72, 75, 79, 86, 90, 97, 101, 105, 108, 113, 119 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☐ Claim(s) 15, 19, 41, 54, 56, 60, 62, 64, 66, 76, 122-137 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 15, 19, 41, 54, 56, 62 and 76 have been amended. Claim 63 has been canceled. Claims 122-137 have been added. Claims 1, 2, 6, 15, 19, 36, 38, 41, 47, 53, 54, 56, 60, 62, 64, 66, 68, 69, 71, 72, 75, 76, 79, 86, 90, 97, 101, 105, 108, 113, 119, 122-137 are pending. Claims 1, 2, 6, 36, 38, 47, 53, 68, 69, 71, 72, 75, 79, 86, 90, 97, 101, 105, 108, 113, 119, drawn to non-elected inventions, are withdrawn from consideration. Claims 15, 19, 41, 54, 56, 60, 62, 64, 66, 76, 122-137 are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 16, lines 14 and 15. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. Claims 135 and 136 are objected to under 37 CFR 1.75 as being substantial duplicates of claims 64 and 66, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

5. Claim 60 is objected to because of the following informalities: The typographical error of "claims 64" as opposed to claim 64. Appropriate correction is required.

6. Claims 15, 19, 123, 62, 122, 127, 126, 125, 129 are objected to for including non-elected inventions. Applicant has Elected Group VIII, in Paper No. 15, filed February 28, 2002:

VIII Claim 15 in part, claim 19 (part 2 and part 3) and claims 41, 54, 56, 60, 62, 63, 64, 66 and 76, drawn to isolated nucleic acids, kits comprising nucleic acids, pharmaceutical compositions comprising nucleic acids,

expression vectors, host cells and pharmaceutical compositions comprising host cells, classified in class 536, subclasses 23.5, 24.31, 24.33, class 514, subclass 44 and class 435, subclasses 69.3, 70.1, 320.1 and 372.

Claims 15 and 19 were included with this group to the extent that they read on a pharmaceutical composition which is a nucleic acid. When given the broadest reasonable interpretation, the instant claims 15 and 19 read on pharmaceutical compositions comprising polypeptides encoded by nucleic acids. Applicant argues that the amended claims do not read on non-nucleic acid species. This has been considered but not found persuasive, as the specific language of claim 15 is "A pharmaceutical preparation comprising an agent which when administered to a subject enriches selectively the presence of complexes of an MHC molecule and a cancer associated antigen". This preamble does not limit the claims to the nucleic acids specified in sections (a) through (c) because the agent which selectively enriches could be a polypeptide or the nucleic acid. Correction is required.

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 60, 62, 63, 64, 66, 135, 136 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 60, 62 and 63 are drawn to an expression vector comprising a nucleic acid. Claims 64, 66 135 and 136 are drawn to a host cell transformed or transfected with an expression vector. The claims can be construed as reading on a human being comprising said expression vector as a result of a gene therapy procedure. Amendment of the claims to recite "An isolated expression vector" and "An isolated host cell" would overcome this rejection.

9. The rejection of claim 56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claim 56 has been amended to recite "a fragment of a nucleic acid molecule having a nucleotide sequence as set forth as SEQ ID NO:23, of sufficient length to represent a sequence unique within the mouse or human genomes, and which identifies it as a nucleic acid encoding a cancer associated antigen". First, it is unclear how the length of a sequence or its uniqueness can identify said sequence as encoding a cancer associated antigen as specified by part a. Second, it is unclear how the uniqueness of said sequence is to be determined. Third, the proviso that "the isolated nucleic acid molecule includes a sequence which is not identical to the nucleic acid sequence represented by GenBank Accession number AI024421 renders the metes and bounds of the claim to be undefined. Applicant argues that "Although Gene Bank is continuously updated with new sequences and changes to sequences, all changes are documented and recorded as a function of time". This has been considered but not found persuasive. The claims are now excluding Accession Number AI024421.1 in favor of of the Accession Number AI024421 which encompasses all future version of AI024421.1. The metes and bounds of the claims cannot be determined as all the future sequences which will follow version 1 of said Accession Number are unknown.

10. Claims 63, 76 and 137 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "NA Group 1 molecule" in claim 63 lacks proper antecedent basis in claim 62.

Claim 76 recites "wherein the contiguous segments are non-overlapping". It is unclear what "non-overlapping" is in reference to.

Claim 137 is vague and indefinite in the recitation of "wherein the pair of nucleic acid molecules is constructed and arranged to selectively amplify an isolated nucleic acid". It is unclear what constitutes said construction and said arrangement

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 15 (19, 123, 62, 122, 128, 127, 126, 125, 129) 41 (62, 124, 130, 131, 132), 56, 62, 133, 134, 76, 137 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter.

Claim 56 has been amended to recite the Gene Bank Accession Number AI024421. The claim The specification and claims as filed recited the negative limitation, "provided that the fragment includes a sequence of contiguous nucleic acids which is not identical to any sequence selected from the group consisting of (1)sequences having the GenBank Accession numbers of Table 8". Table 8 lists "AI024421.1" as having sequence homology to SEQ ID NO:23. Claims drawn to GenBank Accession No. AI024421 are now encompassing all future versions of said Accession Number. This represents a broadening of scope of the instant claims not supported by the specification or claims at the time of filling.

Claim 137 has been added with the amendment filed on August 8, 2002. Original claim 78 was drawn to the kit of claim 76 wherein the pari of isolated nucleic acid molecules is constructed and arranged to selectively amplify an isolated nucleic acid molecule that is a NA 3 Group molecule. The specification defines an NA 3 Group molecule on page 14, lines 8-16 as

selected from the group consisting of (a) previously unknown nucleic acids encoding for a cancer associated antigen precursor, (b) deletions, additions and substitutions which code for a respective cancer associated antigen precursor, (c) nucleic acid molecules that differ from the nucleic acid molecules of (a) or (b) due to differences in coding sequence due to the degeneracy of the genetic code, and (d) complements of (a), (b) or (c). It appears that an NA Group 3 molecule is confined to previously unknown nucleic acids which encode a cancer associated antigen precursor, as well as variants and degenerate coding sequences thereof. Claim 137 is more broadly drawn to encompass any nucleic acid, including nucleic acid known at the time of filling which encode cancer associated antigen precursors. The specification provides no support for a kit wherein the pair of nucleic acids are constructed and arranges as to selectively amplify any nucleic acid sequence, beyond those of NA Group 3.

(B) As drawn to inadequate written description

Claims 15 (19, 123, 62, 122, 128, 127, 126, 125, 129). Claim 41 (62, 124, 130, 131, 132), claim 76 (137). Claim 15 is drawn to a pharmaceutical preparation comprising as agent which enriches selectively the presence of complexes of an MHC molecule and a cancer associated antigen, wherein the cancer associated antigen is a fragment of a cancer associated antigen precursor encoded by the nucleic acid molecule comprising a comprising a nucleic acid molecule selected from the group consisting of (a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence as set forth as SEQ ID NO:23 and which code for the cancer associated antigen precursor, (b) degenerate coding sequences of part (a), and (c) complements of (a) and (b). Claims 19, 62, 122, 123 and 125-129 are dependent on claim 15.

Claim 41 is drawn to a pharmaceutical composition comprising an isolated nucleic acid molecule selected from the group consisting of (a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence as set forth as SEQ ID NO:23 and which code for the cancer associated antigen precursor, (b) degenerate coding

sequences of part (a), and (c) complements of (a) and (b), and (d) fragments of (a), (b), or (c) which code for a polypeptide which, or a portion of which, binds an MHC molecule to form a complex recognized by an autologous antibody or lymphocyte. Claims 62, 124, 130, 131 and 132 are dependent upon claim 41.

Claim 76 is drawn to a kit comprising a pair of isolated nucleic acid molecules each of which consists essentially of a molecule selected from the group consisting of (a) a 12-32 nucleotide contiguous segment of the nucleotide sequence of a nucleic acid molecule which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence as set forth as SEQ ID NO:23 and which code for the cancer associated antigen precursor, (b) degenerate coding sequences of part (a), and (c) complements of (a) and (b), wherein the contiguous segment are non-overlapping. Claim 137 is dependent on claim 76.

Claim 14, 41 and 76 are drawn to a genus of nucleic acid sequences by virtue of reliance on the limitation "stringent hybridization". It is noted that the specification provides examples of stringent hybridization conditions on page 15, lines 21-32, however, these examples do not constitute a limiting definition of stringent hybridization conditions. The claims are drawn to a genus of nucleic acid molecules which are highly variant because numerous structural alterations are tolerated within the genus. Structural and functional attributes which are characteristic of the genus are missing from the claims, the only requirement being that the nucleic acid encodes any cancer associated antigen precursor . When given the broadest reasonable interpretation, the claims read on any cancer associated antigen precursor such as MAGE, BAGE, GAGE and RAGE as well as other listed on page 21, lines 1-5. Further, the specification states on page 13, lines 19-21 state that homologs and alleles of the cancer associated antigen precursors can be identified by conventional techniques. The specification provides no teachings as to the location of mutational sites which would not alter the function of the encoded polypeptide, nor does the specification provide examples of any polymorphic sites. The general knowledge in the art concerning alleles does not provide any indication of how one allele is representative of unknown

alleles. One of skill in the art would conclude that applicant failed to disclose a representative number of species of the claimed invention and because the genus is highly variant the disclosure of SEQ ID NO:23 is not representative of the claimed genus. Therefore applicant was not in possession of the claimed genus.

13. Claims 15, 19, 41, 60, 62, 64, 66, 122-132, 135-137 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to pharmaceutical compositions comprising nucleic acids, vectors and host cells. The specification states on page 12, lines 4-7 that " the invention also involves the use of genes, gene products, fragments thereof...in the preparation of medicaments. A particular medicament is for treating cancer, preferably bladder cancer, colon cancer, lung cancer, breast cancer or hepatoma". Thus the application contemplates the administration of pharmaceutical compositions comprising nucleic acids and host cells in gene therapy for the treatment of cancer. The specification is not enabling for said pharmaceutical compositions for the reasons set forth below.

(A) As drawn to gene therapy

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in

vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

It is well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the method of using the instant pharmaceutical compositions and host cells thereof in the administration of antigen presenting cells transfected or infected ex vivo (page 9, line 27 to page 10, line 5). Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states

that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

Further, even if the specification were enabling for the delivery of the disclosed nucleic acids, the specification is not enabling for a therapeutic use of the expressed polypeptide for the reasons set forth below.

(B) As drawn to nucleic acids encoding peptides which evoke a efficacious response against cancer

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the

blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10) and that mice are devoid of these antibodies (page 315, second column, lines 9-13). Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion"). In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. The instant specification teaches that the peptide encoded by the claimed nucleic acids was recognized by allogenic antisera (page 17, lines 23-25). However, for the reasons stated above, the presence of an endogenous antibody to a cancer associated antigen can be deleterious to immunotherapy comprising the administration of said

antigen, or the nucleic acid encoding said antigen. These references discussed above serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

It is well know in the art that primary tumors in situ are often heterogeneous with respect to MHC presentation (for example, the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102), and the effect of the claimed vaccine upon such a heterogenous tumor has not been demonstrated by the specification. Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teach that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous clones within tumor cells which are so de-differentiated that they no longer express cancer cell specific molecules (abstract).

The art recognizes that T-cell are subject to clonal deletion within the thymus of a host and that this mechanism eliminates t-cell which are reactive with self-antigens. The specification teaches that the polypeptide encoded by SEQ ID NO:23 is a self antigen, rather than a mutated self antigen, as it is expressed on normal tissues as well as cancerous tissues. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor

cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the instant case, the antigens are known self antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the treatment of cancer as a genus of diseases comprising in particular bladder cancer, colon cancer, lung cancer, breast cancer or hepatoma (page 12, lines 4-7), it cannot be anticipated that a T-cell clone would be available after thymic selection in patients having cancers of all types, wherein said T-cell would react with said antigen in the context of HLA-A24 or any other MHC molecule. It is also recognized in the art that the isolation of CTL from a cancer patient which can lyse target cells in

vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis of target cells expressing DAGE antigen in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

It is noted that the broad genus of cancer types (e.g. bladder cancer, colon cancer, lung cancer, breast cancer or hepatoma) to which the specification asserts the claimed pharmaceutical compositions would be useful in treating would not be expected to initiate or maintain the same growth kinetics. It is unclear whether all patients having a cancer expressing the disclosed antigen would have T-cells which were specific from the disclosed antigen, as the art teaches that the presence of a small number of tumor cells or the presence of a large number of tumor cells gives rise to tolerance (Paul, page 1166, second column, lines 19-23 under the heading "Sneaking Through"). Based on this observation, it is reasonable to conclude that a small number of slow growing tumor cells would elicit tolerance, and a large number of rapidly growing tumor cells would also elicit tolerance in line with the bi-phasic response reported by Paul. Thus, it appears that the interaction of the tumor cells with the host can produce tolerance by means of clonal deletion within the thymus of said host.

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering tumor antigen precursors or tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed pharmaceutical preparations comprising nucleic acids would

generate CTLs which lyse the cells of a tumor in situ, and it cannot be predicted that all patients having cancer expressing the polypeptide encoded by SEQ ID NO:23 would all have a T-cell repertoire that would include a T-cell specific for the disclosed self antigen. Without said T-cell in the repertoire of the host, presentation of said antigen by an antigen-presenting cell after vaccination with the disclosed polypeptide or cell expressing said disclosed polypeptide would not evoke a T-cell response, as the appropriate T-cell would not be available in the periphery to be activated by said antigen-presenting cell. Thus, without a demonstration that the administration of the claimed polypeptides or cells expressing said polypeptides overcomes immunosuppression of the host, the rapid growth of the target tumor cells, failure to access the tumor because of the stromal barrier and tolerance induction in the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells, one of skill in the art would be subject to undue experimentation in order to use the claimed polypeptides of cells expressing said polypeptides as vaccines as all of these factors would need to be tested in vivo.

Further, it is noted that claims 15, 41 and 127 are drawn to nucleic acid which hybridize to SEQ ID NO:23 and which code for cancer associated antigen precursors. Section (c) of said claims specifically recite the limitation "complements" in reference to the above nucleic acids encoding the tumor associated antigen precursor. It is unclear how a pharmaceutical composition comprising a nucleic acid which hybridizes to SEQ ID NO:23 could be used in the instant invention because said anti-sense sequence would not be expected to encode a fragment of the amino acid sequence encoded by SEQ ID NO:23, and therefore would not be expected to associate with an MHC molecule in a manner that is similar to the fragments of SEQ ID NO:23. As such, only said complements would provide the requisite T cell epitopes which are required for an efficacious immune response.

Given the unreliable state of the art with respect to gene therapy in general, and tumor immunotherapy with tumor derived peptides, and given the lack of teachings regarding the

coding sequence of anti-sense SEQ ID NO:23 it is concluded that one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the disclosed methods of treatment.

14. The rejection of claims 15, 19, 41, 54, 56, 60, 62, 64, 66, 76 and 137 under 35 U.S.C. 102(b) as being anticipated by Jacobs et al (WO 98/45437) as evidenced by Accession number AAV88163 is maintained for reasons of record. .The rejection of claim 131, 132, 133, 134 and 135 are also rejected under 35 U.S.C. 102(b) as being anticipated by Jacobs et al (WO 98/45437) as evidenced by Accession number AAV88163.

Applicant argues that the amended claims are not anticipated by Jacobs et al because language regarding variants and fragments has been removed. This has been considered but not found persuasive. Jacobs et al disclose a nucleic acid sequence which hybridizes to SEQ ID NO:23 as evidence by AAV88163 wherein said nucleic acid sequence encodes a cancer associated antigen and pharmaceutical compositions comprising expression vectors directing the expression of the disclosed polynucleotide and host cells comprising said expression vectors (page 69, lines 14-25, page 59, line 28 to page 60, line 3). Jacobs et al teach a host cell further comprising a nucleic acid encoding an MHC molecule (page 69, line 29 to page 70, line 3). Jacobs et al disclose kits comprising non-overlapping primers for SEQ ID NO:23 for PCR detection (page 63, lines 18-26 and page 64, lines 15-16). The sequence disclosed by Jacobs et al is not identical to SEQ ID NO:23, however, the claims do not recite hybridization conditions which would exclude AAV88163, and the specification does not define "stringent hybridization conditions". It is noted that the examples of hybridization conditions as listed on page 15, lines 21-32 cannot be construed as a limiting definition.

15. Claims 54 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by The New England Biolabs Catalog (1993-1994, page 91). Claim 54 is drawn in part to a complement of a

nucleic acid molecule which hybridizes to SEQ ID NO:23 under stringent conditions and which codes for a cancer associated antigen precursor. Claim 56 is drawn in part to the complement of a fragment of a nucleic acid molecule having a nucleotide sequence as set forth as SEQ ID NO:23. The New England Biolabs Catalog discloses Random Primers on page 91 which would be a complement of SEQ ID NO:23 or a complement of a nucleic acid which would hybridize to SEQ ID NO:23.

16. All other rejections and objections as set forth in Paper No. 17 are withdrawn.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

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Patent Examiner, Group 1642

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